08/918407
A.A.#30

1. Document ID: US 20010014734 A1

L9: Entry 1 of 23

File: PGPB

Aug 16, 2001

PGPUB-DOCUMENT-NUMBER: 20010014734
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010014734 A1

TITLE: PROGRESSION ELEVATED GENE-3 AND USES THEREOF

PUBLICATION-DATE: August 16, 2001
US-CL-CURRENT: 536/23.1; 424/93.1, 435/320.1

APPL-NO: 09/ 052753
DATE FILED: March 31, 1998
CONTINUED PROSECUTION APPLICATION: CPA

RELATED-US-APPL-DATA:

RLAN	RLFD	RLPC	RLKC	RLAC
09052753	Mar 31, 1998	UNKNOWN	A1	US
PCT/US98/05793	Mar 20, 1998	GRANTED		US
PCT/US98/05793	Mar 20, 1998			US
08821818	Mar 21, 1997			US
6146877				

IN: FISHER, PAUL B.

AB: This invention provides a vector suitable for introduction into a cell, comprising:
a) an inducible PEG-3 regulatory region; and b) a gene encoding a product that causes or may be
induced to cause the death or inhibition of cancer cell growth. In addition, this invention
further provides the above-described vectors, wherein the inducible PEG-3 regulatory region is a
promoter. This invention further provides the above-described vectors, wherein the gene encodes
an inducer of apoptosis. In addition, this invention provides the above-described vectors,
wherein the gene is a tumor suppressor gene. In addition, this invention provides the
above-described vectors, wherein the gene encodes a viral replication protein. This invention
also provides the above-described vectors, wherein the gene encodes a product toxic to cells or
an intermediate to a product toxic to cells. In addition, this invention provides the
above-described vectors, wherein the gene encodes a product causing enhanced immune recognition
of the cell. This invention further provides the above-described vectors, wherein the gene
encodes a product causing the cell to express a specific antigen.

L9: Entry 1 of 23

File: PGPB

Aug 16, 2001

DOCUMENT-IDENTIFIER: US 20010014734 A1
TITLE: PROGRESSION ELEVATED GENE-3 AND USES THEREOF

DETX:
[0675] To define the mode of action of PEG-3 a 5' DNA sequence containing the promoter region of
this gene has been isolated and analyzed. The PEG-3-Promoter (PEG-Prom) (.about.2.1 kb) has been
linked to a luciferase reporter gene (PEG-Prom-Luc) and evaluated for expression in various cell
types. Elevated levels of PEG-Prom-Luc activity are apparent in transformed rodent cells displaying
a progressed transformed phenotype, DNA damaged rodent and human cells, oncogenically transformed
rodent cells and histologically distinct human cancer cells (including metastatic melanoma,
glioblastoma multiforme and carcinomas of the breast, cervix, colon, lung, nasopharyngx and
prostate). On the basis of the selective activity of the PEG-Prom for cancer cells, genetic vectors
are being constructed that display targeted expression of growth arresting and apoptosis-inducing
genes or genes encoding an enzyme permitting activation of a toxic product in cancer cells.
Additionally, genetic vectors can be constructed using the CURE protocol that target the expression
of molecules on the surface of only cancer cells permitting the directed therapy of cancer using
immunological reagents (monoclonal antibodies, cytotoxic T-cells, TILs, etc.) or toxic chemicals.
These novel vectors are the basis for the CURE (Cancer Utilized Reporter Execution) protocol (FIG.
32). As one application of CURE, recombinant adenoviruses are being constructed that permit the
efficient delivery of CURE vectors into cells. These vectors are designed as CIRAs (Cancer
Inhibitory Recombinant Adenoviruses) and they contain the PEG-Prom driving expression of target
genes, including wild-type p53 (wt p53), melanoma differentiation associated gene-7 (mda-7),
adenovirus E1A and E1B (Ad E1A and E1B) or herpes simplex type 1 thymidine kinase gene (HSV TK)
(FIG. 32). When cancer cells are infected with the CIRAs, the appropriate genes are activated
resulting in a direct growth inhibition or apoptosis (wt p53 or mda-7), cell death following
adenovirus replication (Ad E1A and E1B) or cell death following administration of gangcyclovir (HSV
TK).

2. Document ID: US 6297366 B1

L9: Entry 2 of 23

File: USPT

Oct 2, 2001

US-PAT-NO: 6297366
DOCUMENT-IDENTIFIER: US 6297366 B1
TITLE: ING-encoded p33ING1 protein as a mediator of p53 signaling pathway in mammalian cells
DATE-ISSUED: October 2, 2001

US-CL-CURRENT: 536/23.5; 435/325, 536/23.1, 536/24.1

APPL-NO: 9/ 006783
DATE FILED: January 14, 1998

IN: Gudkov; Andrei, Garkavstev; Igor, Riabowol; Karl

AB: The invention relates to a novel tumor suppressor gene, termed ING, genetic
suppressor elements derived from this gene, and the protein produced by expression of this gene,
known as p33.sup.ING1. The invention provides methods for characterizing mammalian cells on the
basis of whether such cells express the ING gene, and embodiments of such methods directed at
malignant or pre-malignant tissues in an animal for assaying the risk of developing malignant
disease by the animal.

L9: Entry 2 of 23

File: USPT

Oct 2, 2001

DOCUMENT-IDENTIFIER: US 6297366 B1
TITLE: ING-encoded p33ING1 protein as a mediator of p53 signaling pathway in mammalian cells

DEPR:
The present invention is based on the discovery that the biological effects of ING1 and p53 gene
expression are interrelated and require the activity of both genes. Specifically, the present
inventors have discovered that neither of these two genes can, on it's own, cause growth inhibition
when the other one is suppressed. Expression of both genes in a mammalian cell results in normal
growth regulation anchorage-dependent growth and apoptosis as a response to irreversible DNA damage
and other cellular insult. Inhibition of expression of either gene results in a loss of cellular
growth control, anchorage-independent growth, inhibition of apoptosis and resistance to radiation
and cytotoxic drugs.

3. Document ID: US 6235891 B1

L9: Entry 3 of 23

File: USPT

May 22, 2001

US-PAT-NO: 6235891
DOCUMENT-IDENTIFIER: US 6235891 B1
TITLE: Glucocorticoid receptor agonist and decreased PP5
DATE-ISSUED: May 22, 2001

US-CL-CURRENT: 536/24.5; 435/325, 435/366, 435/375, 435/6, 435/91.1, 536/23.1, 536/24.3

APPL-NO: 9/ 282736
DATE FILED: March 31, 1999

IN: Honkanen; Richard E.

AB: A composition comprises a glucocorticoid receptor agonist and a compound which
decreases levels of active human serine/threonine protein phosphatase 5 protein in cells. The
glucocorticoid receptor agonist is dexamethasone and the compound is an antisense
oligonucleotide of about 8 to 50 nucleotides in length which is targeted to a nucleic acid
encoding human serine/threonine protein phosphatase 5. The composition is useful in a method of
enhancing glucocorticoid activity, and in a method of enhancing the inhibition of
hyperproliferation of cells where the inhibition is by contacting the cells with a compound
which decreases levels of active human serine/threonine protein phosphatase 5 protein in cells.
The compound is thus useful to enhance glucocorticoid therapy and to enhance inhibition of
hyperproliferation relating to PP5.

L9: Entry 3 of 23

File: USPT

May 22, 2001

DOCUMENT-IDENTIFIER: US 6235891 B1
TITLE: Glucocorticoid receptor agonist and decreased PP5

DEPR:
In addition to a possible direct effect on p53, in A549 cells PP5 prevents the phosphorylation of
p53 by inhibiting the expression of a GR inducible p53 kinase or a GR inducible signaling cascade
that culminates in the hyperphosphorylation of p53. Thus, the hyperphosphorylation of a relatively
small amount of constitutively expressed p53 appears to be sufficient for the propagation of a
steroid hormone induced signaling cascade that inhibits cell growth, while both enhanced
phosphorylation and enhanced expression of p53 contribute to the propagation of a DNA damage induced
response (Levine 1997; Agarwal et al. 1998). Although the data suggest that p53 is a necessary
component of a signaling cascade elicited by glucocorticoids that leads to G1-growth arrest, it does
not exclude the existence of additional GR-induced mechanisms that lead to the induction of
p21.sup.Waf1/Cip1. Indeed, since high concentrations (.gtoreq.100 nM) of dexamethasone can still
partially inhibit A549 cell growth even when the expression of p53 is suppressed with ISIS 8345, it
is tempting to speculate that cells which are acutely sensitive to the antiproliferative effects of
glucocorticoids derive their acute sensitivity from a synergistic effect where dexamethasone induces
the expression of p21.sup.Waf1/Cip1 by both p53 dependent and p53 independent (Cram et al. 1998)
mechanisms. Furthermore, because the data suggest that PP5 is a key negative regulator of
glucocorticoid-mediated induction of p21.sup.Waf1/Cip1, the increased expression of PP5 that is
observed during log phase growth may prove important for the regulation of cellular proliferation.
That is, by inhibiting GR-mediated growth arresting pathways, an increase in PP5 expression may
facilitate the actions of growth promoting compounds. Alternatively, increased PP5 expression may
result in the abatement of glucocorticoid maintained growth arrest, and, thus, induce, or contribute
to the initiation of, a proliferative response. Either way, this suggests that aberrations in the
regulation of PP5 expression may contribute to neoplastic transformation and is consistent with 1)
the observation that PP5 expression is higher in tumor cells than in "normal" differentiated cells;
and 2) that the inhibition of PP5 expression alone inhibits cell growth in p53 wild-type tumor cells
(Zuo et al. 1998). More importantly, since mutations in p53 are associated with about 50% of all
human cancers, the data presented here demonstrating that p53 participates in GR-hormone induced
G1-growth arrest suggest that the loss of glucocorticoid-induced growth arrest may be an important
component of the aberrant proliferative behavior of p53 defective tumor cells. Clinically the
presence or absence of functional p53 may provide insight into why some hematologic malignancies

respond to GR treatment, while others with a similar phenotype do not. If so, the p53 status of a
cancer cell may also prove predictive for determining the effectiveness of glucocorticoid
incorporation into the chemotherapy regimen used in the treatment of GR-responsive cancers.
Compounds that inhibit PP5 activity may also have significant therapeutic value in the treatment of
patients with defects in glucocorticoid signaling pathways or pathways involved in p53 signaling.

4. Document ID: US 6214821 B1

L9: Entry 4 of 23

File: USPT

Apr 10, 2001

US-PAT-NO: 6214821
DOCUMENT-IDENTIFIER: US 6214821 B1
TITLE: Methods and composition for the inhibition of cancer cells
DATE-ISSUED: April 10, 2001

US-CL-CURRENT: 514/214.02; 514/283

APPL-NO: 9/ 262452
DATE FILED: March 4, 1999

PARENT-CASE:
This application claims the benefit of U.S. Provisional Application No. 60/076,960 filed Mar. 5,
1998.

IN: Daoud; Sayed S.

AB: Pharmaceutical compositions comprising a topoisomerase I inhibitor, such as
camptothecin or a camptothecin analog, and a staurosporine such as 7-hydroxystaurosporine,
together with a pharmaceutically acceptable carrier or diluent are provided. In other aspects,
methods of inhibiting the growth of cancer cells are provided by contacting the cells with an
cell growth inhibiting amount of a topoisomerase I inhibitor, such as camptothecin or a
camptothecin analog, and a staurosporine, such as 7-hydroxystaurosporine, while protecting
normal cells from topoisomerase I inhibitor induced cytotoxicity.

L9: Entry 4 of 23

File: USPT

Apr 10, 2001

DOCUMENT-IDENTIFIER: US 6214821 B1
TITLE: Methods and composition for the inhibition of cancer cells

DEPR:
UCN-01 (7-hydroxystaurosporine) (FIG. 1) is entering phase I clinical trials following evidence of
preclinical activity (Akinaga S. et al., "Antitumor activity of UCN-01, a selective inhibitor of
protein kinase C, in murine and human tumor models," Cancer Res. 51:4888-4892 (1991); and Lush R. M.
et al., "Surprising pharmacokinetics of UCN-01 in patients with refractory neoplasms may be due to
high degree of protein binding," Proc. AACR 38:4029 (1997)). The drug was originally isolated from a
strain of Streptomyces as a protein kinase C (PKC)-selective inhibitor (Takahashi I. et al.,
"UCN-01, a selective inhibitor of protein kinase C from Streptomyces," J Antibiot. 40:1782-1784
(1987)), although recent evidence suggest that PKC inhibition is unlikely to be directly responsible
for the UCN-01 cytotoxicity (Seynaeve C. M. et al., "Cell cycle arrest and growth inhibition by the
protein kinase antagonist UCN-01 in human breast carcinoma cells," Cancer Res. 53:2081-2086 (1993);
and Monks A. et al., "Synergistic interactions between UCN-01 and various anti-cancer agents in
vitro: relationship to p53 function," Proc. AACR 38:2137 (1997)). UCN-01 has been shown to abrogate
S and G.sub.2 checkpoints following DNA damage, preferentially in cells with disrupted p53 function
compared to wild-type p53. Thus when the drug was combined with radiation or cisplatin, a
synergistic interaction was only observed in cells with disrupted p53 function (Russell, K. J. et
al., "Abrogation of the G.sub.2 checkpoint results in differential radiosensitization of G.sub.1
checkpoint-deficient and competent cells," Cancer Res. 55:1639-1642 (1995); and Bunch R. T. et al.,
"Enhancement of cisplatin-induced cytotoxicity by 7-hydroxystaurosporine (UCN-01), a new G.sub.2
-checkpoint inhibitor," Clinical Cancer Res. 2:791-797 (1996)). The data from Examples 1-3
demonstrates that UCN-01 at sublethal doses can enhance CPT-induced cytotoxicity in tumor cells as
compared to normal endothelial cells (FIG. 2). When this enhancement was assessed according to
inhibition of cell growth, the IC.sub.50 values obtained for CPT in the presence and absence of 100
nM UCN-01 during 24 exposure of GI 101A cells were 300 nM and 10 nM, respectively; and for MDA-231
cells were 200 nM and 5 nM (FIGS. 2A and 2B). There was no enhancement of CPT-induced cytotoxicity
in normal endothelial cells as clearly indicated in FIG. 2C.

DEPR:
The potentiating effect of UCN-01 on CPT-induced cytotoxicity in tumor cells with disrupted p53
function raises the question as whether this phenomenon is additive or synergistic. To address this
question, the outcome of the drug combination (growth and proliferation inhibition) was assessed
using the median-effect analysis (Chou T-C. et al. "Quantitative analysis of dose-effect
relationships: The combined effects of multiple drugs or enzyme inhibitors," Adv. Enzyme Regul.
22:27-55 (1984)). The antiproliferative activity (DNA synthesis) of CPT on breast cancer cells with
disrupted p53 is more pronounced than its growth inhibition effect (Jones C. B. et al., "Sensitivity
to camptothecin of human breast cancer cells and normal bovine endothelial cells, in vitro," Cancer
Chemother. Pharmacol. (in press, 1997)). Thus when growth inhibition of the drug combination was
analyzed a synergistic cytotoxic effect was clearly indicated in both cell lines, as shown in FIG.
3A; however, antagonistic interaction was observed with the antiproliferative activity of the drug
combination (FIG. 3B). This effect indicates that UCN-01 is counteracting CPT-induced inhibition of
DNA synthesis by increasing the rate of DNA synthesis in tumor cells. Thus the DNA content of
treated cells was determined by flow cytometry (FIG. 4). As expected, UCN-01 is preferentially
abrogating only the DNA damage dependent activation of S/G.sub.2 checkpoint induced by CPT.
Acceleration of the passage of the tumor cells through the S phase of the cell cycle was observed
when cells were incubated with sublethal doses of UCN-01, thereby increasing the cytotoxic activity
of CPT. This hypothesis is supported by the results of [.sup.3 H]-thymidine incorporation assays
(FIG. 3B) that showed UCN-01 was able to eliminate suppression of DNA synthesis and thus

antagonistic interaction was observed. While the normal endothelial cells showed a loss of S phase
arrested cells with UCN-01 treatment, they accumulated in G.sub.0 /G.sub.1 (FIG. 4C) and were
relatively resistant to the cytotoxicity of the drug combination (FIG. 2C). This was as expected
from normal cells expressed wild-type p53. Thus the cell cycle response of the normal cells to CPT
and UCN-01 was markedly different than that of the tumor cells, and may be responsible for their
lower drug sensitivity.

5. Document ID: US 6211334 B1

L9: Entry 5 of 23

File: USPT

Apr 3, 2001

US-PAT-NO: 6211334
DOCUMENT-IDENTIFIER: US 6211334 B1
TITLE: Cell-cycle regulatory proteins, and uses related thereto
DATE-ISSUED: April 3, 2001

US-CL-CURRENT: 530/350; 435/6, 435/69.7

APPL-NO: 8/ 346147
DATE FILED: November 29, 1994

PARENT-CASE:
RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No. 08/306,511 filed
Sep. 14, 1994, now U.S. Pat. No. 5,962,316 which is a continuation-in-part of U.S. Ser. No.
08/248,812 filed May 25, 1994, now U.S. Pat. No. 5,889,169 which is a continuation-in-part of U.S.
Ser. No. 08/227,371 filed Apr. 14, 1994, which is a continuation-in-part of U.S. Ser. No. 08/154,915
filed Nov. 18, 1993, which is a continuation-in-part of U.S. Ser. No. 07/991,997 filed Dec. 17,
1992, now abandoned which is a continuation-in-part of U.S. Ser. No. 07/963,308 filed Oct. 16, 1992
now abandoned. The teachings of U.S. Ser. No. 08/306,511, now U.S. Pat. No. 592,316 Ser. No.
08/248,812, now U.S. Pat. No. 5,889,169 Ser. Nos. 08/227,371, 08/154,915, 07/991,997, now abandoned
Ser. No. 07/963,308 now abandoned and related PCT publication US93/09945 are incorporated herein by
reference.

IN: Beach; David H., Serrano; Manuel, Hannon; Gregory J.

AB: The present invention relates to the discovery in eukaryotic cells, particularly
mammalian cells, of a novel family of cell-cycle regulatory proteins ("CCR-proteins"). As
described herein, this family of proteins includes a polypeptide having an apparent molecular
weight of 16 kDa, and a polypeptide having an apparent molecular weight of approximately 15 kDa,
each of which can function as an inhibitor of cell-cycle progression, and therefore ultimately
of cell growth. Thus, similar to the role of p21 to the p53 checkpoint, the subject CCR-proteins
may function coordinately with the cell-cycle regulatory protein, retinoblastoma (RB).
Furthermore, the CCR-protein family includes a protein having an apparent molecular weight of
13.5 kDa (hereinafter "p13.5"). The presumptive role of p13.5, like p16 and p15, is in the
regulation of the cell-cycle.

L9: Entry 5 of 23

File: USPT

Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6211334 B1
TITLE: Cell-cycle regulatory proteins, and uses related thereto

BSPR:
The role of RB as a tumor-suppressor protein in cell-cycle control is believed to be similiar to
that of p53. However, whereas p53 is generally believed to be responsive to such indigenous
environmental cues as DNA damage, the RB protein is apparently involved in coordinating cell growth
with exogenous stimulus that normally persuade a cell to cease proliferating, such as diffusible
growth inhibitors. In normal cells, RB is expressed throughout the cell cycle but exists in multiple
phosphorylated forms that are specfic for certain phases of the cycle. The more highly
phosphorylated forms are found during S and G.sub.2 /M, whereas the underphosphorylated forms are
the primary species seen in G.sub.1 and in the growth arrested state. Base on these observations, it
has been argued that if RB is to have a regulatory (suppressive) activity in the cell-cycle, this
activity must be regulated at the post-translational level. Accordingly, underphosphorylated RB
would be the form with growth-suppressive acitivty, since this form is prevalent in G1 and growth
arrested cells.

6. Document ID: US 6147056 A

L9: Entry 6 of 23

File: USPT

Nov 14, 2000

US-PAT-NO: 6147056
DOCUMENT-IDENTIFIER: US 6147056 A
TITLE: Use of locally applied DNA fragments
DATE-ISSUED: November 14, 2000

US-CL-CURRENT: 514/44; 424/450, 514/43, 514/45, 514/46, 514/47

APPL-NO: 9/ 048927
DATE FILED: March 26, 1998

PARENT-CASE:
RELATED APPLICATION(S) This application is a Continuation-in-Part of U.S. National Phase of
PCT/US96/08386 filed Jun. 3, 1996, and assigned U.S. application Ser. No. 08/952,697, filed Dec. 6,
1997, which is a Continuation-in-Part of application Ser. No. 08/467,012 filed Jun. 6, 1995, now
U.S. Pat. No. 5,955,059 the entire teachings of which are incorporated herein by reference.

IN: Gilchrest; Barbara A., Yaar; Mina, Eller; Mark

AB: Methods of treatment or prevention of hyperproliferative diseases or pre-cancerous
conditions affecting epithelial cells, such as psoriasis, vitiligo, atopic dermatitis, or
hyperproliferative or UV-responsive dermatoses, hyperproliferative or allergically mediated
diseases of other epithelia and methods for reducing photoaging or for

prophylaxis against or
reduction in the likelihood of the development of skin cancer, are disclosed.

L9: Entry 6 of 23
File: USPT
Nov 14, 2000

DOCUMENT-IDENTIFIER: US 6147056 A
TITLE: Use of locally applied DNA fragments

DEPR:
The DNA fragments, deoxynucleotides, dinucleotides, or dinucleotide dimers, or agent that increases
p53 activity, are applied to (introduced into or contacted with) the cells of interest in an
appropriate manner. The "cells of interest", as used herein, are those cells which may become
affected or are affected by the hyperproliferative disease or precancerous condition, or cells which
are affected by DNA-damaging conditions such as UV irradiation or exposure to DNA damaging chemicals
such as benzo(a)pyrene. Specifically encompassed by the present invention are epithelial cells,
including melanocytes and keratinocytes, as well as oral, respiratory, bladder and cervical
epithelial cells. As demonstrated herein the methods and compositions of the present invention
inhibit growth of epithelial cells from numerous sources.

7. Document ID: US 6087377 A

L9: Entry 7 of 23
File: USPT
Jul 11, 2000

US-PAT-NO: 6087377
DOCUMENT-IDENTIFIER: US 6087377 A
TITLE: Tamoxifen as a therapy to reduce irinotecan hydrochloride-induced diarrhea
DATE-ISSUED: July 11, 2000

US-CL-CURRENT: 514/324; 514/648

APPL-NO: 9/ 329554
DATE FILED: June 10, 1999

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation of U.S. application Ser.
No. 09/028,779 filed Feb. 24, 1998, now U.S. Pat. No. 5,955,466, which claims the benefit of
provisional application U.S. Ser. No. 60/039,185, filed Feb. 27, 1997, under 35 USC 119(e)(i).

IN: Ulrich; Roger G.

AB: The present invention provides a method for preventing or decreasing diarrhea
associated with irinotecan administration comprising the administration of tamoxifen at least
two cell cycles prior to irinotecan administration.

L9: Entry 7 of 23
File: USPT
Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6087377 A
TITLE: Tamoxifen as a therapy to reduce irinotecan hydrochloride-induced diarrhea

DEPR:
Treatment of human colon adenocarcinoma HT-29 cells with SN-38 showed >90% growth inhibition
(IC.sub.90) at a concentration of 10 nM. Flow cytometric analysis of growth-arrested cells revealed
that replication was blocked in the G.sub.2 phase of the cell cycle. From this arrest point, cells
did not recover but instead underwent programmed cell death (apoptosis). As the HT-29 cells
arrested, levels of p53 were upregulated as determined by Western immunoblot techniques, likely in
response to sensing DNA damage since PCNA levels were also increased. However, the p53 expressed by
HT-29 cells is a mutant (inactive) form hence p21 is not upregulated; we have been unable to detect
p21 in these cells. These experiments show that CPT-11 (SN-38) induces apoptosis in HT-29 cells in a
p53-independent manner from the G.sub.2 phase of the cells cycle.

8. Document ID: US 6057427 A

L9: Entry 8 of 23
File: USPT
May 2, 2000

US-PAT-NO: 6057427
DOCUMENT-IDENTIFIER: US 6057427 A
TITLE: Antibody to cytokine response gene 2(CR2) polypeptide
DATE-ISSUED: May 2, 2000

US-CL-CURRENT: 530/388.23; 424/130.1, 424/139.1, 424/145.1, 530/387.1, 530/387.9, 530/388.1,
530/389.2

APPL-NO: 8/ 652446
DATE FILED: June 5, 1996

PARENT-CASE:
This application is a U.S. national-phase application of PCT International Application No.
PCT/US96/08992, under 35 U.S.C. .sctn.371, which is a continuation-in-part of U.S. Ser. No.
08/330,108, filed Oct. 27, 1994, now U.S. Pat. No. 5,795,752 which is a continuation of U.S. Ser.
No. 08/104,736, filed Aug. 10, 1993, abandoned, which is a continuation of U.S. Ser. No. 07/796,066,
filed Nov. 20, 1991, abandoned.

PCT-DATA:
APPL-NO
DATE-FILED
PUB-NO
PUB-DATE
371-DATE
102(E)-DATE
PCT/US96/08992
June 5, 1996
Jun 5, 1996
Jun 5, 1996

IN: Smith; Kendall A., Beadling; Carol

AB: Disclosed are an isolated antibody or antibody fragment that

selectively binds a
polypeptide encoded by Cytokine Response gene 2 (CR2), and in particular, selectively binds to a
first polypeptide having the sequence of residues 1-60 of SEQ. ID No: 4. Also disclosed is a
composition containing the antibody or antibody fragment and a diluent or carrier. Also
disclosed are methods, using the present antibody or antibody fragment, of isolating or
purifying a peptide comprising an amino acid sequence of residues 1-60 of SEQ. ID No: 4 or an
antibody binding fragment thereof that is at least 10 to 30 amino acids long, or a fusion
protein comprising any of these.

L9: Entry 8 of 23

File: USPT

May 2, 2000

DOCUMENT-IDENTIFIER: US 6057427 A
TITLE: Antibody to cytokine response gene 2(CR2) polypeptide

BSPR:
This gene belongs to a family of small nuclear-localizing gene products. Two other members of this
family, GADD45 and MyD118, have been identified. GADD45 was cloned from human fibroblasts induced by
UV irradiation (Papathanasiou, M. A. et al., Mol. Cell Biol. 11(2): 1009-1016 (1991)). This protein
is regulated by p53 and suppresses growth of cells by binding to PCNA, a co-factor required for DNA
polymerase 8 activity. (Smith, M. L. et al., Science 266: 1376-1380 (1994)). MyD118 was cloned from
M1D+ myeloid precursors following induction of terminal differentiation and growth arrest by IL6.
(Abdollahi, A. et al., Oncogene 6: 165-167 (1991)). At the nucleotide level, CR6 is about 65%
homologous to GADD45. At the protein level, CR6 is about 54% homologous to GADD45. At the nucleotide
level, CR6 is about 66% homologous to MyD118. At the protein level, CR6 is about 53% homologous to
MyD118. The CR6 protein is expressed only in testes, ovary and prostate, and its expression is
suppressed by elevated cAMP. By analogy to it's homology to GADD45 and MyD118, the CR6 gene product
most likely plays a role in DNA replication. Thus far, experiments have indicated that CR6
expression is not induced by agents that damage DNA, such as UV light. Moreover, CR6 does not bind
to PCNA. However, CR6 does promote DNA replication in vitro, and it is likely to be a novel
CD-factor necessary for DNA replication. Therefore, the CR6 gene product can be used to identify
inhibitors of DNA replication which can be used as anti-proliferative agents, e.g., in the treatment
of cancer.

9. Document ID: US 6054467 A

L9: Entry 9 of 23

File: USPT

Apr 25, 2000

US-PAT-NO: 6054467
DOCUMENT-IDENTIFIER: US 6054467 A
TITLE: Down-regulation of DNA repair to enhance sensitivity to P53-mediated apoptosis
DATE-ISSUED: April 25, 2000

US-CL-CURRENT: 514/309; 435/7.1, 435/7.23, 514/456, 514/617, 514/619

APPL-NO: 8/ 675887
DATE FILED: July 5, 1996

IN: Gjerset; Ruth A.

AB: The present invention details methods for the treatment of cancer. In particular it
concerns the induction of apoptosis in cancer cells following treatment with inhibitors of DNA
repair in combination with p53. Treatment of glioblastoma and breast tumor cells with inhibitors
of DNA repair induced growth suppression that was a result of p53-mediated apoptosis. Thus it
appears that inhibitors of DNA repair in combination with p53 is involved in restoration of
p53-mediated apoptosis.

L9: Entry 9 of 23

File: USPT

Apr 25, 2000

DOCUMENT-IDENTIFIER: US 6054467 A
TITLE: Down-regulation of DNA repair to enhance sensitivity to P53-mediated apoptosis

DEPR:
In the first instance, viability of 9L rat glioblastoma cells infected with either .beta.gal
adenovirus or p53 adenovirus, and treated one day later in the absence or presence of 50 .mu.M
cisplatin was measured seven days after administration of cisplatin (FIG. 5). 9L rat glioblastoma
cells infected with p53 adenovirus exhibited a significant decrease in viability compared to 9L
cells infected with .beta.gal adenovirus when exposed to cisplatin. The viability of 9L rat
glioblastoma cells infected with either .beta.gal adenovirus or p53 adenovirus in the absence of
cisplatin did not significantly decrease. Thus tumor cells that have sustained DNA damage are more
susceptible to growth suppression by p53.

DEPR:
In the second instance, T47D breast cancer cells were infected with .beta.gal-adenovirus or p53
adenovirus and treated with SR11220 or cisplatin or both. SR11220 is a synthetic retinoid that
specifically down-regulates AP-1. Cisplatin is a common chemotherapeutic agent that creates DNA
adducts in cells. T47D breast cancer cells infected with p53 adenovirus were slightly sensitive to
the effects of p53, in comparison to T47D breast cancer cells infected with .beta.gal-adenovirus
(FIG. 2). Upon treatment of p53 adenovirus infected T47D cells with 10.sup.-8 M SR11220, a further
reduction in viability was shown. Treatment of p53 adenovirus infected T47D cells with 10 .mu.M
cisplatin had an even greater effect on the reduction in viability. Treatment of p53 adenovirus
infected T47D cells with a combination if 10.sup.-8 M SR11220 and 10 .mu.M cisplatin further reduced
the viability of the tumor cells. In contrast the viability of T47D cells infected with the
.beta.gal adenovirus control was not reduced significantly after treatment with SR11220, cisplatin
or a combination thereof. Thus the combined effects of a DNA damaging agent and an inhibitor of DNA
repair significantly sensitize tumor cells to growth suppression by p53.

DEPR:
The effects of increasing levels of cisplatin on the growth characteristics of

the following tumor
cells were tested: T47D breast carcinoma, T98G glioblastoma, and 9L rat glioblastoma. Cell viability
was measured in T47D breast carcinoma cells after infection with wild-type p53 adenovirus and
subsequent treatment with cisplatin two days post-infection (FIG. 7A). Cell viability decreased with
increasing doses of cisplatin whereas control T47D breast carcinoma cells infected with
.beta.gal-adenovirus were significantly more refractory to the DNA damaging effects of cisplatin.
Similarly, cisplatin treatment of T98G glioblastoma cells infected with wild-type p53 adenovilLis
sensitized the tumor cells to growth suppression in a dose dependent manner (FIG. 7B). T98G
glioblastoma cells infected with .beta.gal adenovirus exhibited a slightly reduce growth rate in
response to increasing levels of cisplatin.

DEPR:
Tumor cells stably modified with constructs expressing wild-type p53 were also sensitized to the
effects of cisplatin. Cell viability of T98G glioblastoma cells stably modified with a vector
containing wild-type p53, pLp53RNL was reduced in a dose dependent manner after treatment with
increasing doses of cisplatin (FIG. 7C.) Control T98G glioblastoma cells stably modified with vector
only, pLNRL, were more resistant to the effects of cisplatin treatment. Similarly, cisplatin
treatment of 9L rat glioblastoma cells stably modified by a vector containing wild-type p53,
pCEPp53, significantly reduced the viability of the tumor cells in a dose dependent manner as
compared to 9L glioblastoma cells stably modified with the control vector pCEP4 (FIG. 7D.). In
general then, as cisplatin-induced DNA damage increases, tumor cell growth suppression mediated by
p53 concomitantly increases.

10. Document ID: US 6051376 A

L9: Entry 10 of 23
File: USPT
Apr 18, 2000

US-PAT-NO: 6051376
DOCUMENT-IDENTIFIER: US 6051376 A
TITLE: Uses of mda-6
DATE-ISSUED: April 18, 2000

US-CL-CURRENT: 435/6; 435/69.1, 436/501, 514/2, 514/44

APPL-NO: 8/ 316537
DATE FILED: September 30, 1994

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 08/143,576 filed Oct. 27,
1993 now U.S. Pat. No. 5,643,761, the contents of which are hereby incorporated by reference.

IN: Fisher; Paul B., Jiang; Hongping

AB: This invention provides a method of generating a subtracted cDNA library of a cell
comprising: a) generating a cDNA library of the cell; b) isolating double-stranded DNAs from the
cDNA library; c) releasing the double-stranded cDNA inserts from the double-stranded DNAs; d)
denaturing the isolated double-stranded cDNA inserts; e) hybridizing the denatured
double-stranded cDNA inserts with a labelled single-stranded nucleic acid molecules which are to
be subtracted from the cDNA library; and f) separating the hybridized labeled single-stranded
nucleic acid molecule from the double-stranded cDNA inserts, thereby generating a subtracted
cDNA library of a cell. This invention also provides different uses of the subtracted library.

L9: Entry 10 of 23
File: USPT
Apr 18, 2000

DOCUMENT-IDENTIFIER: US 6051376 A
TITLE: Uses of mda-6

DEPR:
Cell-cycle regulation results from the ordered activation of a series of related enzymes referred to
as cyclin-dependent kinases (CDKs) (42). In normal cells, CDKs are predominantly found in multiple
quaternary complexes, consisting of CDK, a cyclin, proliferating cell nuclear antigen (PCNA) and the
p21 protein (43,44). p21 controls CDK activity, thereby affecting cell-cycle control and growth in
mammalian cells (43-50). Using human glioblastoma cells containing an inducible wild-type p53 tumor
suppressor gene and subtraction hybridization, a gene called WAF1 (wild-type p53-activated fragment
1) that encodes an M21,000 protein was identified (49,50). WAF1 is the same p21-encoding gene
identified using the two-hybrid system as a potent CDK inhibitor, referred to as CPI1
(Cdk-interacting protein 1) (46). p.21 levels have been shown to increase in senescent cells (gene
referred to as sdi-1; senescent cell-derived inhibitor) (51) and overexpression of p21 inhibits the
growth of tumor cells (46,49,51). Treatment of wild-type p53 containing cells with DNA damaging
agents results in elevated wild-type p53 protein and increased p21 levels (51). In this context, p21
may directly contribute to G.sub.1 growth arrest and apoptosis resulting in specific target cells
after induction of DNA damage (51). Recent studies also demonstrate that p21 can: directly inhibit
PCNA-dependent DNA replication in the absence of a cyclin/CDK; and inhibit the ability of PCNA to
activate DNA polymerase .delta. by directly interacting with PCNA (52). These studies indicate that
p21 is an important component of growth control, cell-cycle progression, DNA replication and the
repair of damaged DNA.

DEPR:
The human p21 cyclin-dependent kinase (Cdk)-interacting protein CIP1 (Xiong et al., 1993b); Harper
et al., 1993), and the mouse CAP20 homologue (Gu et al., 1993), is a ubiquitous inhibitor of cyclin
kinases and an integral component of cell cycle control. This gene is identical to the WAF1
(wild-type (wt) p53 activated factor-1) gene identified following induction by wt p53 protein
expression in a human glioblastoma multiforme cell line (El-Deiry et al., 1993). p21 has also been
independently cloned as a consequence of induction of senescence in normal human foreskin fibroblast
cells, SDI1 (senescent cell-derived inhibitor-1) (Noda et al., 1994), and during the process of
terminal cell differentiation in human melanoma cells, mda-6 (Jiang and Fisher, 1993; Jiang et al.,
1994). p21 is a nuclear localized protein that is inducted by DNA damage and during apoptosis in
specific cell types as a function of wt p53 activation (El-Deiry et al., 1993,

1994). These studies
suggest that p21 may be an important downstream mediator of wt p53-induced growth control in
mammalian cells (El-Deiry et al., 1993, 1994). Somewhat paradoxical data indicates that WAF1/CIP1 is
induced as an immediate-early gene following mitogenic stimulation of growth arrested cells in a
p53-independent manner (Michieli et al., 1994). Applicants presently demonstrate that mda-6
(WAF1/CIP1/SDI1) expression is also induced by mechanistically diverse acting agents resulting in
macrophage/monocyte (TPA and Vit D3) or granulocyte (RA and DMSO) differentiation in human
promyelocytic leukemia cells (Collins, 1987), HL-60, that lack endogenous p53 genes (Wolf and
Rotter, 1985). Using differentiation-resistant variants (Homma et al., 1986; Mitchell et al., 1986),
a direct correlation is found between the early induction of mda-6 expression and the onset of
specific programs of differentiation in HL-60 cells. Applicants' results indicate that sustained p21
expression can be maintained in the absence of wt p53 protein and elevated levels of p21
(WAF1/CIP1/SDI1) mRNA and protein correlate with growth suppression and differentiation induction in
a p53-independent manner in HL-60 cells.

DEPR:
The specific genomic changes that mediate melanoma development and progression remain to be
elucidated (Herlyn, 1990; Kerbel, 1990; Clark, 1991). To directly approach this question and to
begin to identify and clone genes involved in growth control and differentiation in human melanoma
cells applicants have used subtraction hybridization (Jiang & Fisher, 1993; Jiang et al., 1994a).
cDNA libraries were constructed from untreated HO-1 human melanoma cells and these cDNAs were
subtracted from cDNA libraries prepared from HO-1 cells treated with the combination of IFN-.beta.
plus MEZ that induces an irreversible loss of proliferative ability and terminal differentiation
(Fisher et al., 1985; Jiang & Fisher, 1993; Jiang et al., 1993, 1994a). This approach has resulted
in the identification of several novel mda cDNA clones that display enhanced expression as a
function of growth suppression and induction of terminal differentiation in human melanoma cells
(Jiang & Fisher, 1993; Jiang et al., 1994a). In the present study applicants have analyzed mda-6
(Jiang & Fisher, 1993; Jiang et al., 1994a), whose open reading frame sequence (FIG. 30) is
identical to the genes WAF1, CIP1 and SDI1 (El-Deiry et al., 1993; Harper et al., 1993; Noda et al.,
1994). WAF1 was cloned using a strategy designed to identify inducible down-stream genes that are
directly controlled by and might mediate the growth suppressing activity of the tumor suppressor
gene p53 (El-Deiry et al., 1993). Introduction of WAF1 cDNA into human brain, lung and colon tumor
cell cultures results in growth suppression (El-Deiry et al., 1993). In addition, WAF1 is induced by
DNA damage in wild-type p53-containing cells and during the process of p53-associated G.sub.1 arrest
or apoptosis (El-Deiry et al., 1994). CIP1 was identified using an improved two-hybrid system and
encodes a 21-kDa product that is a potent inhibitor of cyclin-dependent kinases (Harper et al.,
1993). CIP1 induces growth suppression in normal diploid fibroblasts but only marginally inhibits
growth in SV40-transformed diploid fibroblasts (Harper et al., 1993). SDI1 was identified and cloned
from senescent human fibroblasts using an expression screening strategy designed to detect cDNAs
that could prevent young fibroblasts from initiating DNA synthesis (Noda et al., 1994). The current
studies indicate that mda-6 (WAF1/CIP1/SDI1) expression is also related to growth regulation in
human melanoma cells and its reduced expression may contribute to the progressive changes observed
in the evolution of melanocytes into metastatic melanomas.

11. Document ID: US 6043030 A

L9: Entry 11 of 23 File: USPT Mar 28, 2000

US-PAT-NO: 6043030
DOCUMENT-IDENTIFIER: US 6043030 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto
DATE-ISSUED: March 28, 2000

US-CL-CURRENT: 435/6; 435/14, 435/7.1, 435/7.72

APPL-NO: 8/ 581918
DATE FILED: January 2, 1996

PARENT-CASE:
RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No. 08/497,214 filed
Jun. 30, 1995, which is a continuation-in-part of U.S. Ser. No. 08/346,147 filed Nov. 29, 1994,
which is a continuation-in-part of U.S. Ser. No. 08/306,511 filed Sep. 14, 1994, now U.S. Pat. No.
5,962,316, which is a continuation-in-part of U.S. Ser. No. 08/248,812 filed May 25, 1994 and now
U.S. Pat. No. 5,889,169, which is a continuation-in-part of U.S. Ser. No. 08/227,371 filed Apr. 14,
1994, which is a continuation-in-part of U.S. Ser. No. 08/154,915 filed Nov. 18, 1993, which is a
continuation-in-part of U.S. Ser. No. 07/991,997 filed Dec. 17, 1992 and now abandoned. The
teachings of U.S. Ser. Nos. 08/497,214, 08/346,147, 08/306,511, 08/248,812, 08/227,371, 08/154,915
and 07/991,997 are incorporated herein by reference.

IN: Beach; David H., Demetrick; Douglas J., Serrano; Manuel, Hannon; Gregory J.

AB: The present invention relates to the discovery in eukaryotic cells, particularly
mammalian cells, of a novel family of cell-cycle regulatory proteins ("CCR-proteins"). As
described herein, this family of proteins is characterized by four ankyrin repeats and the
ability to bind to a cyclin dependent kinase (CDK). The family includes a polypeptide having an
apparent molecular weight of 16 kDa, and a polypeptide having an apparent molecular weight of
approximately 15 kDa, each of which can function as an inhibitor of cell-cycle progression, and
therefore ultimately of cell growth. Thus, similar to the role of p21 to the p53 checkpoint, the
subject CCR-proteins may function coordinately with the cell-cycle regulatory protein,
retinoblastoma (RB).

L9: Entry 11 of 23 File: USPT Mar 28, 2000

DOCUMENT-IDENTIFIER: US 6043030 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto

BSPR:
The role of RB as a tumor-suppressor protein in cell-cycle control is believed to be similiar to
that of p53. However, whereas p53 is generally believed to be responsive to such indigenous
environmental cues as DNA damage, the RB protein is apparently involved in coordinating cell growth
with exogenous stimulus that normally persuade a cell to cease proliferating, such as diffusible
growth inhibitors. In normal cells, RB is expressed throughout the cell cycle but exists in multiple
phosphorylated forms that are specfic for certain phases of the cycle. The more highly
phosphorylated forms are found during S and G.sub.2 /M, whereas the underphosphorylated forms are
the primary species seen in G.sub.1 and in the growth arrested state. Base on these observations, it
has been argued that if RB is to have a regulatory (suppressive) activity in the cell-cycle, this
activity must be regulated at the post-translational level. Accordingly, underphosphorylated RB
would be the form with growth-suppressive acitivty, since this form is prevalent in G1 and growth
arrested cells.

12. Document ID: US 5968821 A

L9: Entry 12 of 23
File: USPT
Oct 19, 1999

US-PAT-NO: 5968821
DOCUMENT-IDENTIFIER: US 5968821 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto
DATE-ISSUED: October 19, 1999

US-CL-CURRENT: 435/325; 435/320.1, 435/455, 435/6, 435/69.1, 536/23.1

APPL-NO: 8/ 893274
DATE FILED: July 15, 1997

PARENT-CASE:
RELATED APPLICATIONS This application is a continuation application of Ser. No. 08/306,511 filed on
Sep. 14, 1994, which is a continuation-in-part of U.S. Ser. No. 08/248,812 filed May 25, 1994 and
entitled "Cell-cycle Regulatory Protein, and Uses Related Thereto", which is a continuation-in-part
of U.S. Ser. No. 08/227,371 filed Apr. 14, 1994 and entitled "Cell-cycle Regulatory Protein, and
Uses Related Thereto", which is a continuation-in-part of U.S. Ser. No. 08/154,915 filed Nov. 18,
1993 and entitled "Cyclin Complex Rearrangements and Uses Related Thereto", which is a
continuation-in-part of U.S. Ser. No. 07/991,997 filed Dec. 17, 1992 and entitled "Cyclin Complex
Rearrangements and Uses Related Thereto", abandoned, which is a continuation-in-part of U.S. Ser.
No. 07/963,308 filed Oct. 16, 1992 and entitled "D-Type Cyclin and Uses Related Thereto". The
teachings of U.S. Ser. Nos. 08/248,812, 08/227,371, 08/154,915, 07/991,997, 07/963,308 and related
PCT publication US93/09945 are incorporated herein by reference.

IN: Beach; David H., Demetrick; Douglas J., Serrano; Manuel, Hannon; Gregory J.

AB: The present invention relates to the discovery in eukaryotic cells, particularly
mammalian cells, of a novel family of cell-cycle regulatory proteins ("CCR-proteins"). As
described herein, this family of proteins includes a polypeptide having an apparent molecular
weight of 16 kDa, and a polypeptide having an apparent molecular weight of approximately 15 kDa,
each of which can function as an inhibitor of cell-cycle progression, and therefore ultimately
of cell growth. Thus, similar to the role of p21 to the p53 checkpoint, the subject CCR-proteins
may function coordinately with the cell-cycle regulatory protein, retinoblastoma (RB).
Furthermore, the CCR-protein family includes a protein having an apparent molecular weight of
13.5 kDa (hereinafter "p13.5"). The presumptive role of p13.5, like p16 and p15, is in the
regulation of the cell-cycle.

L9: Entry 12 of 23
File: USPT
Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968821 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto

BSPR:
The role of RB as a tumor-suppressor protein in cell-cycle control is believed to be similiar to
that of p53. However, whereas p53 is generally believed to be responsive to such indigenous
environmental cues as DNA damage, the RB protein is apparently involved in coordinating cell growth
with exogenous stimulus that normally persuade a cell to cease proliferating, such as diffusible
growth inhibitors. In normal cells, RB is expressed throughout the cell cycle but exists in multiple
phosphorylated forms that are specfic for certain phases of the cycle. The more highly
phosphorylated forms are found during S and G.sub.2 /M, whereas the underphosphorylated forms are
the primary species seen in G.sub.1 and in the growth arrested state. Base on these observations, it
has been argued that if RB is to have a regulatory (suppressive) activity in the cell-cycle, this
activity must be regulated at the post-translational level. Accordingly, underphosphorylated RB
would be the form with growth-suppressive acitivty, since this form is prevalent in G1 and growth
arrested cells.

13. Document ID: US 5962316 A

L9: Entry 13 of 23
File: USPT
Oct 5, 1999

US-PAT-NO: 5962316
DOCUMENT-IDENTIFIER: US 5962316 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto
DATE-ISSUED: October 5, 1999

US-CL-CURRENT: 435/325; 424/185.1, 424/93.21, 435/320.1, 435/455, 435/6, 435/69.1, 514/44, 530/350,
536/23.1, 536/23.4, 536/23.5, 536/24.1

APPL-NO: 8/ 306511
DATE FILED: September 14, 1994

PARENT-CASE:
RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No. 08/248,812 filed
May 25, 1994 and entitled "Cell-cycle Regulatory Protein, and Uses Related Thereto", which is a
continuation-in-part of U.S. Ser. No. 08/227,371 filed Apr. 14, 1994 and entitled "Cell-cycle
Regulatory Protein, and Uses Related Thereto", which is a continuation-in-part of U.S. Ser. No.
08/154,915 filed Nov. 18, 1993 and entitled "Cyclin Complex Rearrangements and Uses Related
Thereto", which is a continuation-in-part of U.S. Ser. No. 07/991,997 filed Dec. 17, 1992 and
entitled "Cyclin Complex Rearrangements and Uses Related Thereto", now abandoned, which is a
continuation-in-part of U.S. Ser. No. 07/963,308 filed Oct. 16, 1992 and entitled "D-Type Cyclin and
Uses Related Thereto". The teachings of U.S. Ser. Nos. 08/248,812, 08/227,371, 08/154,915,
07/991,997, 07/963,308 and related PCT publication US 93/09945 are incorporated herein by reference.

IN: Beach; David H., Demetrick; Douglas J., Serrano; Manuel, Hannon; Gregory J.

AB: The present invention relates to the discovery in eukaryotic cells, particularly
mammalian cells, of a novel family of cell-cycle regulatory proteins ("CCR-proteins"). As
described herein, this family of proteins includes a polypeptide having an apparent molecular
weight of 16 kDa, and a polypeptide having an apparent molecular weight of approximately 15 kDa,
each of which can function as an inhibitor of cell-cycle progression, and therefore ultimately
of cell growth. Thus, similar to the role of p21 to the p53 checkpoint, the subject CCR-proteins
may function coordinately with the cell-cycle regulatory protein, retinoblastoma (RB).
Furthermore, the CCR-protein family includes a protein having an apparent molecular weight of
13.5 kDa (hereinafter "p13.5"). The presumptive role of p13.5, like p16 and p15, is in the
regulation of the cell-cycle.

L9: Entry 13 of 23

File: USPT

Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962316 A
TITLE: Cell-cycle regulatory proteins, and uses related thereto

BSPR:
The role of RB as a tumor-suppressor protein in cell-cycle control is believed to be similar to that
of p53. However, whereas p53 is generally believed to be responsive to such indigenous environmental
cues as DNA damage, the RB protein is apparently involved in coordinating cell growth with exogenous
stimulus that normally persuade a cell to cease proliferating, such as diffusible growth inhibitors.
In normal cells, RB is expressed throughout the cell cycle but exists in multiple phosphorylated
forms that are specific for certain phases of the cycle. The more highly phosphorylated forms are
found during S and G.sub.2 /M, whereas the underphosphorylated forms are the primary species seen in
G.sub.1 and in the growth arrested state. Base on these observations, it has been argued that if RB
is to have a regulatory (suppressive) activity in the cell-cycle, this activity must be regulated at
the post-translational level. Accordingly, underphosphorylated RB would be the form with
growth-suppressive activity, since this form is prevalent in G1 and growth arrested cells.

14. Document ID: US 5955466 A

L9: Entry 14 of 23

File: USPT

Sep 21, 1999

US-PAT-NO: 5955466
DOCUMENT-IDENTIFIER: US 5955466 A
TITLE: Tamoxifen as a therapy to reduce irinotecan hydrochloride-induced diarrhea
DATE-ISSUED: September 21, 1999

US-CL-CURRENT: 514/280; 514/651

APPL-NO: 9/ 028779
DATE FILED: February 24, 1998

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application claims the benefit of provisional
application U.S. Ser. No. 60/039,185, filed Feb. 27, 1997, under 35 USC 119(e)(i).

IN: Ulrich; Roger G.

AB: The present invention provides a method for preventing or decreasing diarrhea
associated with irinotecan administration comprising the administration of tamoxifen at least
two cell cycles prior to irinotecan administration.

L9: Entry 14 of 23

File: USPT

Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5955466 A
TITLE: Tamoxifen as a therapy to reduce irinotecan hydrochloride-induced diarrhea

DEPR:
Treatment of human colon adenocarcinoma HT-29 cells with SN-38 showed >90% growth inhibition
(IC.sub.90) at a concentration of 10 nM. Flow cytometric analysis of growth-arrested cells revealed
that replication was blocked in the G.sub.2 phase of the cell cycle. From this arrest point, cells
did not recover but instead underwent programmed cell death (apoptosis). As the HT-29 cells
arrested, levels of p53 were upregulated as determined by Western immunoblot techniques, likely in
response to sensing DNA damage since PCNA levels were also increased. However, the p53 expressed by
HT-29 cells is a mutant (inactive) form hence p21 is not upregulated; we have been unable to detect
p21 in these cells. These experiments show that CPT-11 (SN-38) induces apoptosis in HT-29 cells in a
p53-independent manner from the G.sub.2 phase of the cells cycle.

15. Document ID: US 5886149 A

L9: Entry 15 of 23

File: USPT

Mar 23, 1999

US-PAT-NO: 5886149
DOCUMENT-IDENTIFIER: US 5886149 A
TITLE: P53 response genes
DATE-ISSUED: March 23, 1999

US-CL-CURRENT: 530/350; 536/23.5

APPL-NO: 8/ 754108
DATE FILED: November 20, 1996

PARENT-CASE:
This application is a divisional of application Ser. No. 08/274,281 filed Jul. 12, 1994, now U.S.
Pat. No. 5,667,987 which is incorporated herein by reference.

IN: Buckbinder; Leonard, Talbott; Randy, Seizinger; Bernd R., Kley; Nikolai

AB: This present invention concerns polypeptide molecules comprising human p53 response
protein PIGI-1.

L9: Entry 15 of 23

File: USPT

Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5886149 A
TITLE: P53 response genes

DEPR:
Consistent with p53's role in the DNA damage response, we have found that, like WAF1 [El-Deiry et
al., Cancer Res. 54, 1169-1174 (1994)], PIGI-1 is induced by DNA damaging agents such as adriamycin
or ultraviolet irradiation (data not shown), and that this induction correlates with the p53 status
of the cell. Therefore, activation of PIGI-1 could represent an important step in the cellular
growth inhibitory and/or apoptotic response to DNA damage.

16. Document ID: US 5877210 A

L9: Entry 16 of 23

File: USPT

Mar 2, 1999

US-PAT-NO: 5877210
DOCUMENT-IDENTIFIER: US 5877210 A
TITLE: Phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for controlling
cellular proliferation
DATE-ISSUED: March 2, 1999

US-CL-CURRENT: 514/492; 424/178.1, 424/179.1, 424/181.1, 435/184, 435/244, 556/1, 556/42, 556/44

APPL-NO: 8/ 465813
DATE FILED: June 5, 1995

PARENT-CASE:
CROSS-REFERENCES This application is a continuation-in-part of PCT Application Ser. No.
PCT/US95/01234, filed Jan. 30, 1995 and designating the United States, entitled "Use of
Phosphotyrosine Phosphatase Inhibitors or Phosphotyrosine Kinase Activators for Controlling Cellular
Proliferation," by Gary L. Schieven, which was itself a continuation-in-part of U.S. application
Ser. No. 08/189,330, filed Jan. 31, 1994, now U.S. Pat. No. 5,565,491, also entitled "Use of
Phosphotyrosine Phosphatase Inhibitors or Phosphotyrosine Kinase Activators for Controlling Cellular
Proliferation," by Gary L. Schieven. The disclosures of these two prior applications are
incorporated herein in their entirety by this reference.

IN: Schieven; Gary L.

AB: A method of inhibiting the proliferation of B cells by using inhibitors of
phosphotyrosine phosphatase can be used to regulate the immune response and to treat diseases
such as leukemias or lymphomas marked by malignant proliferation of B cells or T cells.
Antitumor activity is seen in vivo against tumors and against tumor cell lines. The use of such
inhibitors can be combined with radiation, which produces a synergistic effect. Several types of
inhibitors can be used, including: (1) compounds comprising a metal coordinate-covalently bound
to an organic moiety that can form a five- or six-membered ring, in which the metal is
preferably vanadium (IV); (2) compounds in which vanadium (IV) is coordinate-covalently bound to
an organic moiety such as a hydroxamate, .alpha.-hydroxypyridinone, .alpha.-hydroxypyrone,
.alpha.-amino acid, hydroxycarbonyl, or thiohydroxamate; (3) coordinate-covalent complexes of
vanadyl and cysteine or a derivative thereof; (4) nonhydrolyzable phosphotyrosine phosphatase
analogues; (5) dephostatin; (6) 4-(fluoromethyl)phenyl phosphate and esterified derivatives; and
(7) coordinate-covalent metal-organic compounds containing at least one oxo or peroxo ligand
bound to the metal, in which the metal is preferably vanadium (V), molybdenum (VI), or tungsten
(VI). Methods of stimulating signaling in T cells and conjugates of a modulator of
phosphotyrosine metabolism with a specific binding partner for a B cell surface antigen are also
disclosed.

L9: Entry 16 of 23

File: USPT

Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5877210 A
TITLE: Phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for controlling
cellular proliferation

DEPR:
The reason for the selectivity of BMLOV effects on B cell versus T cells or other cell types remain
to be identified. B cells might have higher levels of basal tyrosine kinase activity and therefore
require higher levels of PTP activity to maintain most substrates in a non-phosphorylated state,
making the cells more susceptible to PTP inhibition. Alternatively, the PTPs regulating B cell
tyrosine phosphorylation may be more sensitive to BMLOV. It is likely that CD45 plays an important
role since immature B cells negative for CD45 are much more sensitive to apoptosis induced by
anti-IgM stimulation (M. Ogimoto et al., "Negative Regulation of

Apoptotic Death in Immature B Cells
by CD45," Inter. Immunol. 6:647-654 (1994)). The induction of apoptosis in cells by accumulation of
tyrosine phosphorylation requires that the cells have such a signal pathway in place capable of
inducing apoptosis. Although such signal pathways are known in lymphocytes, they have not been
reported for most other cell types, such as colon cells. For example, BMLOV can weakly induce
tyrosine phosphorylation in H3347 carcinoma cells, but the cells do not undergo apoptosis, and there
is no reported example of tyrosine phosphorylation dependent signals inducing apoptosis in colon
cells. The expression of oncogenes and tumor suppressor genes might also be expected to influence
the activity of cells to PTP inhibitor induced apoptosis. HL-60 cells lack an intact p53 gene, while
Raji cells have a mutated p53 allele (M. B. Kastan et al., "Participation of p53 Protein in the
Cellular Response to DNA Damage," Cancer Res. 51:6304-6311 (1991), so wild type p53 does not appear
to be essential for BMLOV induced apoptosis or inhibition of clonogenic cell growth.

levels. The upregulation of p53, in turn, can cause inhibition of cell proliferation or growth, e.g.
can induce quiescence, or can result in cell death, such as by apoptotic mechanisms. Consequently,
the E6AP antisense constructs of the present invention can be used to modulate the function of p53
in order to control of cellular proliferation and/or viability. For example, as described below, the
E6AP antisense constructs of the present invention can be used to inhibit proliferation of
PV-infected and PV-transformed cells. Furthermore, the anti-proliferative activity of the subject
antisense constructs may also be employed in the treatment of other hyperplasias or neoplasias which
arise in p53+ cell populations which contain wild-type p53 (e.g. may function to induce apoptosis),
or mutant p53 (e.g., function to offset a diminishment in p53 activity by increasing the level of
mutant p53). Moreover, such antisense constructs can also be used prophylactically to increase p53
levels and thereby enhance protection against DNA damaging agents (e.g., radiation) or other
cytotoxic agents whenever it is known that exposure to such damaging agents is imminent. For
example, the therapy described below can be used to protect normal cells from cytotoxic agents
administered in the chemotherapeutic treatment of a tumor having a p53.sup.- phenotype.

17. Document ID: US 5858987 A

L9: Entry 17 of 23
File: USPT
Jan 12, 1999

US-PAT-NO: 5858987
DOCUMENT-IDENTIFIER: US 5858987 A
TITLE: E6AP antisense constructs and methods of use
DATE-ISSUED: January 12, 1999

US-CL-CURRENT: 514/44; 435/5, 435/6, 435/91.2, 536/23.1, 536/24.3, 536/24.33, 536/24.5

APPL-NO: 8/ 435637
DATE FILED: May 5, 1995

IN: Beer-Romero; Peggy L., Draetta; Giulio, Rolfe; Mark

AB: The present invention relates to the discovery that antisense nucleic acids
complimentary to an E6AP gene can be used to regulate cellular p53 levels. In general the
invention features E6AP antisense constructs which, by inhibiting E6AP activity, can modulate
cellular p53 levels in both p53+ transformed cells and in normal cells. The invention also
provides methods for treating papillomavirus (PV) induced condition, methods for regulating
cellular p53 levels and methods for regulating cellular proliferation.

L9: Entry 17 of 23
File: USPT
Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858987 A
TITLE: E6AP antisense constructs and methods of use

DEPR:
The present invention derives from the discovery that antisense nucleic acids against the E6AP
message can, by apparently disrupting E6AP expression, cause marked increases in the cellular p53

18. Document ID: US 5846998 A

L9: Entry 18 of 23
File: USPT
Dec 8, 1998

US-PAT-NO: 5846998
DOCUMENT-IDENTIFIER: US 5846998 A
TITLE: Use of phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for
controlling cellular proliferation
DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 514/492; 424/617, 424/646, 435/184, 435/326, 556/1, 556/42, 556/44

APPL-NO: 8/ 669499
DATE FILED: June 18, 1996

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATION(S) This is a continuation-in-part of U.S. patent application
Ser. No. 08/189,330, entitled "Use of Phosphotyrosine Phosphatase Inhibitors or Phosphotyrosine
Kinase Activators for Controlling Cellular Proliferation," filed on Jan. 31, 1994, now U.S. Pat. No.
5,565,491, issued Oct. 15, 1996, and is incorporated by reference herein.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US95/01234	January 30, 1995	WO95/20390	Aug 3, 1995	Jun 18, 1996	Jun 18, 1996

IN: Schieven; Gary L.

AB: A method of inhibiting the proliferation of B cells by using inhibitors of
phosphotyrosine phosphatase can be used to regulate the immune response and to treat diseases
such as leukemias or lymphomas marked by malignant proliferation of B cells or T cells.
Antitumor activity is seen in vivo against tumors and against tumor cell lines. The use o such
inhibitors can be combined with radiation, which produces a synergistic effect. Several types of
inhibitors can be used, including: (1) compounds comprising a metal coordinate-covalently bound
to an organic moiety that can form a five- or six-membered ring, in which the metal is
preferably vanadium (IV); (2) compounds in which vanadium (IV) is coordinate-covalently bound to
an organic moiety such as a hydroxamate, .alpha.-hydroxypyridinone, .alpha.-hydroxypyrone,
.alpha.-amino acid, hydroxycarbonyl, or thiohydroxamate; (3) coordinate-covalent complexes of
cysteine or a derivative thereof; (4) nonhydrolyzable phosphotyrosine analogues; (5)
dephostatin; (6) 4-(fluoromethyl)phenyl phosphate and esterified derivatives; and (7)
coordinate-covalent metal-organic compounds containing at least one oxo or peroxo ligand bound
to the metal, in which the metal is preferably vanadium (V), molybdenum (VI), or tungsten (VI).

L9: Entry 18 of 23

File: USPT

Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5846998 A
TITLE: Use of phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for
controlling cellular proliferation

DEPR:
The reason for the selectivity of BMLOV effects on B cell versus T cells or other cell types remain
to be identified. B cells might have higher levels of basal tyrosine kinase activity and therefore
require higher levels of PTP activity to maintain most substrates in a non-phosphorylated state,
making the cells more susceptible to PTP inhibition. Alternatively, the PTPs regulating B cell
tyrosine phosphorylation may be more sensitive to BMLOV. It is likely that CD45 plays an important
role since immature B cells negative for CD45 are much more sensitive to apoptosis induced by
anti-IgM stimulation (M. Ogimoto et al., "Negative Regulation of Apoptotic Death in Immature B Cells
by CD45," Inter. Immunol. 6:647-654 (1994)). The induction of apoptosis in cells by accumulation of
tyrosine phosphorylation requires that the cells have such a signal pathway in place capable of
inducing apoptosis. Although such signal pathways are known in lymphocytes, they have not been
reported for most other cell types, such as colon cells. For example, BMLOV can weakly induce
tyrosine phosphorylation in H3347 carcinoma cells, but the cells do not undergo apoptosis, and there
is no reported example of tyrosine phosphorylation dependent signals inducing apoptosis in colon
cells. The expression of oncogenes and tumor suppressor genes might also be expected to influence
the activity of cells to PTP inhibitor induced apoptosis. HL-60 cells lack an intact p53 gene, while
Raji cells have a mutated p53 allele (M. B. Kastan et al., "Participation of p53 Protein in the
Cellular Response to DNA Damage," Cancer Res. 51:6304-6311 (1991), so wild type p53 does not appear
to be essential for BMLOV induced apoptosis or inhibition of clonogenic cell growth.

19. Document ID: US 5830723 A

L9: Entry 19 of 23

File: USPT

Nov 3, 1998

US-PAT-NO: 5830723
DOCUMENT-IDENTIFIER: US 5830723 A
TITLE: Method for immortalizing chicken cells
DATE-ISSUED: November 3, 1998

US-CL-CURRENT: 435/467; 435/235.1, 435/325, 435/349, 435/373

APPL-NO: 8/ 696376
DATE FILED: August 13, 1996

IN: Foster; Douglas N., Farris; James A., Foster; Linda K.

AB: This invention relates to the introduction of p53 under the control of the
metallothionein promoter into primary cells to produce immortalized cell lines. The cells are
useful as substrates for viral propagation, as contaminant-free sources for recombinant protein
production, for recombinant virus production and as cell substrates to support primary cells and
improve virus yield during virus propagation.

L9: Entry 19 of 23

File: USPT

Nov 3, 1998

DOCUMENT-IDENTIFIER: US 5830723 A
TITLE: Method for immortalizing chicken cells

DEPR:
The cells of this invention are immortalized by the introduction of p53 under the control of the
inducible metallothionein promoter into preferably primary cells. The nuclear oncogene p53 is one of
the most well studied tumor suppressor genes in part due to the fact that mutations in the p53 gene
contribute in some way to upwards of 50% of all human caners (Levine et al., Nature 351:453-456,
1991). p53 is a cellular phosphoprotein and is frequently present at elevated levels in transformed
cells (De Leo, A. B. et al. Proc. Natl. Acad. Sci 76:2420-2424, 1979). Wild-type p53 appears to
function in a growth suppressive manner (Michalovity et al. Cell 62:671-680, 1990) and p53 arrests
cells at cell cycle checkpoints in response to DNA damage (Kastan, et al. Cancer Res. 51:6304-6311,
1991). The checkpoint function is carried out by the accumulation of p53 and a subsequent induction
of GADD45 (an important excision repair protein), WAF 1 (p21), and MDM2 (which forms a stable
complex with p53) genes. (Kastan, et al. Cell 71:587-597, 1992). This theory is supported by the
observation that mutations in p53 can result in cellular immortalization.

20. Document ID: US 5736318 A

L9: Entry 20 of 23

File: USPT

Apr 7, 1998

US-PAT-NO: 5736318
DOCUMENT-IDENTIFIER: US 5736318 A
TITLE: Method and kit for evaluating human papillomavirus transformed cells
DATE-ISSUED: April 7, 1998

US-CL-CURRENT: 435/5; 424/204.1, 424/277.1, 435/183, 530/395

APPL-NO: 8/ 406248
DATE FILED: March 17, 1995

IN: Munger; Karl, Jones; D. Leanne

AB: The invention provides methods and kits for determining the extent of interaction and/or inactivation between a cyclin/cyclin-dependent kinase inhibitor and the human papilomavirus E7 oncoprotein and thus for evaluating the proliferative state of a transformed cell. Methods for identifying compounds capable of inhibiting the interaction between a cyclin/cyclin-dependent kinase inhibitor and the human papilomavirus E7 oncoprotein, and for inhibiting growth of a human papillomavirus-associated carcinoma cell are also provided.

L9: Entry 20 of 23

File: USPT

Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736318 A
TITLE: Method and kit for evaluating human papillomavirus transformed cells

BSPR:
The p53 and RB tumor suppressors are believed to act by imposing specific blocks to the progression of the cell cycle. If DNA damage occurs in a normal cell, wild type p53 levels increase. By virtue of its ability to bind to DNA in a sequence-specific manner, p53 stimulates expression of a number of genes, for example, the gene encoding a 21 kD protein variously known as p21, WAF1, SDI1, PIC1 and CIP1 (hereinafter referred to as p21.sup.CIP1). The nucleotide and amino acid sequences of p21.sup.CIP1 are set forth in SEQ ID NO:1 and SEQ ID NO:2. The p21.sup.CIP1 protein suppresses growth by inhibiting the activities of a class of protein kinases, the cyclin dependent kinases (cdks), which affect the temporal progression of the cell cycle. In their native state, the cdks form complexes with a regulatory subunit (a cyclin). A large number of cyclins have been identified, as have the specific cdks with which they associate. See, for example, PCT/US/00961 and T. Hunter et al., Cell 79, 573-582 (1994), incorporated herein by reference. When the cyclin/cdk complexes are inhibited by p21.sup.CIP1, cell division is blocked at an important checkpoint in the late G1 phase early in the cell replication cycle. When p21.sup.CIP1 does not inhibit the cyclin/cdk complexes, they stimulate cells to proceed through the cell cycle by phosphorylating and thus modulating the activity of the RB tumor suppressor as well as other regulatory proteins.

21. Document ID: US 5667987 A

L9: Entry 21 of 23

File: USPT

Sep 16, 1997

US-PAT-NO: 5667987
DOCUMENT-IDENTIFIER: US 5667987 A
TITLE: P53 response genes
DATE-ISSUED: September 16, 1997

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 536/23.5

APPL-NO: 8/ 274318
DATE FILED: July 12, 1994

IN: Buckbinder; Leonard, Talbott; Randy, Seizinger; Bernd R., Kley; Nikolai

AB: Nucleic acid sequences, particularly DNA sequences, coding for all or part of p53 response protein PIGI-1, expression vectors containing the DNA sequences, host cells containing the expression vectors, and methods utilizing these materials are disclosed. The invention also concerns polypeptide molecules comprising all or part of p53 response protein PIGI-1, and methods for producing these polypeptide molecules.

L9: Entry 21 of 23

File: USPT

Sep 16, 1997

DOCUMENT-IDENTIFIER: US 5667987 A
TITLE: P53 response genes

DEPR:
Consistent with p53's role in the DNA damage response, we have found that, like WAF1 [El-Deiry et al., Cancer Res. 54, 169-1174 (1994)], PIGI-1 is induced by DNA damaging agents such as adriamycin or ultraviolet irradiation (data not shown), and that this induction correlates with the p53 status of the cell. Therefore, activation of PIGI-1 could represent an important step in the cellular growth inhibitory and/or apoptotic response to DNA damage. Furthermore, novel chemotherapeutics targeting PIGI-1 may replace conventional chemotherapeutic drugs that directly or indirectly target p53. These novel chemotherapeutics should be effective even in tumor cells that lack expression of normal p53.

22. Document ID: WO 9916790 A1, AU 9895655 A

L9: Entry 22 of 23

File: DWPI

Apr 8, 1999

DERWENT-ACC-NO: 1999-263685
DERWENT-WEEK: 199945
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TITLE: Use of p33-ING1 peptides to modulate activity of, isolate or detect p53

PRIORITY-DATA: 1998US-0006783 (January 14, 1998), 1997US-0060138 (September 26, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9916790 A1	April 8, 1999	E	063	C07K014/47
AU 9895655 A	April 23, 1999		000	C07K014/47

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9916790A1	September 24, 1998	1998WO-US18179	
AU 9895655A	September 24, 1998	1998AU-0095655	
AU 9895655A		WO 9916790	Based on

INT-CL (IPC): A61K 38/17; A61K 48/00; C07K 14/47; C12Q 1/68; G01N 33/53

IN: GARKAVTSEV, I, GUDKOV, A, RIABOWOL, K

AB: NOVELTY - Use of p33ING1 peptides for modulating the activity of, isolating or
detecting p53, particularly in the diagnosis and treatment of tumors is new., DETAILED
DESCRIPTION - A novel method of modulating the activity of p53 in a cell comprises administering
a peptide having p33ING1 biological activity or a nucleic acid encoding the peptide to the
cell., INDEPENDENT CLAIMS are also included for the following:, (1) a method for isolating p53
comprising obtaining a biological sample containing p53, contacting the biological sample with a
peptide having p33ING1 biological activity where the p53 binds to the peptide; and isolating the
p53 bound to the peptide;, (2) a method for detecting the presence of p53 in a sample comprising
obtaining a biological sample suspected of containing p53, contacting the biological sample with
a peptide having p33ING1 biological activity under conditions where the p53 binds to the
peptide, and detecting the presence of p53 bound to the peptide;, (3) a method of diagnosing,
screening to detect, or assessing a human sample to determine the risk of developing a malignant
or pre malignant condition in a human comprising:, (a) obtaining a cell or tissue sample from
the human;, (b) assaying the sample to determine ING1 gene expression in the sample;, (c)
comparing ING1 gene expression in the sample with ING1 gene expression in a nonmalignant human
cell or tissue; and, (d) assaying the sample to determine p53 gene expression in the sample,
where a malignant or pre malignant condition is detected or risk of developing the condition is
determined when both p53 and ING1 gene expression in the sample is less than p53 or ING1 gene
expression in the nonmalignant human cells or tissues; and, (4) a composition useful for
modulating p53 activity comprising at least one agent selected from a peptide or protein having
p33ING1 biological activity and a nucleic acid coding for a peptide or protein having p33ING1
biological activity, which provides modulation of p53 activity., USE - The ING1 gene encodes
p33ING1 which can be used to modulate the activity of, isolate or detect p53. Expression of the
ING1 and p53 genes in a mammalian cell results in normal growth regulation anchorage-dependent
growth and apoptosis as a response to irreversible DNA damage and other cellular insult.
Inhibition of expression of either gene results in a loss of cellular growth control, anchorage
independent growth, inhibition of apoptosis and resistance to radiation and cytotoxic drugs.,
The p33ING1 is a component of the p53 signaling pathway that cooperates with p53 in negative
regulation of cell proliferation by modulating p53 dependent transcriptional activation.
Biological function of p53 signaling pathway can therefore be regulated (both enhanced or
suppressed) by modulating p33ING1 activity., The modulation of p33ING1 activity can be used for
the stimulation or restoration of the p53 pathway in anti cancer therapy or for the suppression
of the p53 pathway to defend sensitive tissues from genotoxic stress or for the generation of
immortal cell lines.

L9: Entry 22 of 23 File: DWPI Apr 8, 1999

DERWENT-ACC-NO: 1999-263685
DERWENT-WEEK: 199945
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TITLE: Use of p33-ING1 peptides to modulate activity of, isolate or detect p53

ABTX:
USE - The ING1 gene encodes p33ING1 which can be used to modulate the activity of, isolate or detect
p53. Expression of the ING1 and p53 genes in a mammalian cell results in normal growth regulation
anchorage-dependent growth and apoptosis as a response to irreversible DNA damage and other cellular
insult. Inhibition of expression of either gene results in a loss of cellular growth control,
anchorage independent growth, inhibition of apoptosis and resistance to radiation and cytotoxic
drugs.

23. Document ID: AU 9877050 A, WO 9854201 A1

L9: Entry 23 of 23 File: DWPI Dec 30, 1998

DERWENT-ACC-NO: 1999-059802
DERWENT-WEEK: 199918

TITLE: New isolated human tumour necrosis factor receptor-like protein 8 - used to develop products
for treating e.g. tumours, immunodeficiencies , autoimmune diseases, septic shock, inflammation or
infections

PRIORITY-DATA: 1997US-0048020 (May 29, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9877050 A	December 30, 1998		000	C07H021/04
WO 9854201 A1	December 3, 1998	E	140	C07H021/04

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 9877050A	May 29, 1998	1998AU-0077050	
AU 9877050A		WO 9854201	Based on
WO 9854201A1	May 29, 1998	1998WO-US10980	

INT-CL (IPC): C07H 21/04; C07K 14/705; C12N 15/09; C12N 15/63; C12Q 1/68

IN: MOORE, P A, NI, J

AB: (A) An isolated nucleic acid molecule (NAM) comprising a polynucleotide (PN) having a
nucleotide sequence (NS) at least 95% identical to a sequence selected from: (a) a NS encoding a
TR8 receptor polypeptide comprising an amino acid sequence at positions from -25 to 590, -25 to
211, -5, -3 or +1 to 590 in sequence (II) (615 amino acid sequence given in the specification);
(b) a NS encoding a TR8 receptor polypeptide or a mature TR8 receptor polypeptide having an
amino acid sequence encoded by a cDNA clone contained in ATCC No. 97956; (c) a NS encoding a TR8
extracellular domain, a TR8 transmembrane domain, or a TR8 intracellular domain; and (d) a NS
complementary to any of the NSs above., Also claimed are: (1) an isolated NAM comprising a PN
which hybridises under stringent hybridisation conditions to a PN having a NS as above, where
the PN which hybridises does not hybridise under stringent hybridisation conditions to a PN
having a NS consisting of only A residues or of only T residues; (2) an isolated NAM comprising
a PN which encodes an amino acid sequence of an epitope-bearing portion of a TR8 receptor having
an amino acid sequence as in (a)-(c) of (A); (3) a method for making a recombinant vector
comprising inserting an isolated NAM as in (A) into a vector; (4) a recombinant vector produced
by a method as in (3); (5) a method of making a recombinant host cell comprising introducing a
recombinant vector as in (4) into a host cell; (6) a recombinant host cell produced by a method
as in (5); (7) an isolated NAM comprising a PN having a NS of sequence (I) (2853 bp sequence
given in the specification)encoding a mutant version of (II), where an additional CGC codon is
inserted after nucleotide 72 resulting in insertion of an additional R residue after position 3
in sequence (II), nucleotide 763 is G instead of A, resulting in an amino acid E instead of F at
position 194 in sequence (II), and nucleotide 1583 is G instead of T, resulting in an amino acid
S instead of I at position 487 in sequence (II); (8) an isolated TR8 receptor polypeptide having
an amino acid sequence (II), where an additional R residue is inserted after position 3 in
sequence (II), the amino acid at position 194 in sequence (II) is E instead of F, and an amino
acid at position 487 in sequence (II) is S instead of I; (9) an isolated TR8 polypeptide having
an amino acid sequence at least 95% identical to a sequence selected from: (a) amino acids from
-25 to 590, -25 to 211, or -5, -3 or +1 to 590 of sequence (II); (b) an amino acid sequence of a
TR8 polypeptide or a mature TR8 polypeptide having an amino acid sequence encoded by a cDNA
clone contained in ATCC No. 97956; (c) an amino acid sequence of a TR8 receptor extracellular
domain, a TR8 receptor transmembrane domain, or a TR8 receptor intracellular domain; and (d) an
amino acid sequence of an epitope-bearing portion of any one of the polypeptides of (a)-(c);
(10) an isolated polypeptide comprising an epitope-bearing portion of a TR8 receptor protein,
where the portion is selected from a polypeptide comprising amino acid residues 10-65, 82-185,
211-257, 267-512 or 531-590 of sequence (II); (11) an isolated antibody that binds specifically
to a TR8 receptor polypeptide as in (9)., USE - The TR8 receptor is a tumour necrosis factor
(TNF) receptor like polypeptide. The TR8 receptor is involved in e.g. cell proliferation ,
hematopoeitic development, osteoclast differentiation, and survival of dendritic cells. Soluble
fragments of a TR8 polypeptide can be used to treat herpes simplex viral infection (claimed).
TR8 proteins or agonists or antagonists can be used for treating a disease state associated with
aberrant cell survival (claimed). Diseases associated with increased cell survival, or the
inhibition of apoptosis, include cancers (e.g. follicular lymphomas, carcinomas with p53
mutations, and hormone-dependent tumours), autoimmune disorders (e.g. systemic lupus
erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections
(e.g. herpes viruses, pox viruses and adenoviruses), information graft versus host disease,
acute graft rejection, and chronic graft rejection. Diseases associated with decreased cell
survival, or increased apoptosis, include AIDS, neurodegenerative disorders (e.g. Alzheimer's
disease, Parkinson's disease, Amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar
degeneration), myelodysplastic syndromes (e.g. aplastic anemia), ischemic injury (e.g. as caused
by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (e.g. as
caused by alcohol), septic shock, cachexia and anorexia. The TR8 receptor agonists may be used
to stimulate ligand activities such as inhibition of tumour growth and necrosis of certain
transplantable tumours, or alternatively, the survival of certain cell types (e.g. dendritic
cells (DCs)). The agonists may also be used to stimulate cellular differentiation, e.g. T cells,

osteoclasts, fibroblasts and hematopoietic cell differentiation. Agonists to the TR8 receptor
may also augment TR8's role in the host's defense against microorganisms and prevent related
diseases (infections such as that from Listeria monocytogenes) and Chlamidiae. The agonists may
also be used to protect against the deleterious effects of ionising radiation produced during
course of radiotherapy, such as denaturation of enzymes, lipid peroxidation, and DNA damage.
They may also be used to mediate an anti-viral response, to regulate growth, to mediate the
immune response and to treat immunodeficiencies related to diseases such as HIV by increasing
the rate of lymphocyte proliferation and differentiation. The agonists can also be used to treat
bone fractures, defects and disorders which result in weakened bones such as osteoporosis,
osteomalacia, and age-related loss of bone mass. The antagonists to the polypeptides may be used
to inhibit ligand activities, e.g. stimulation of tumour growth and necrosis of certain
transplantable tumours, and promoting the survival of certain cell types (e.g. DCs). They may
also be used to inhibit cellular differentiation e.g. T-cell, osteoclast, fibroblast, and
hematopoietic cell differentiation. They may also be used to treat autoimmune diseases, e.g.
graft versus host rejection and allograft rejection, T-cell mediated autoimmune diseases such as
AIDS or diabetes or for treating inflammatory diseases e.g. rheumatoid arthritis,
osteoarthritis, psoriasis, septicemia, inflammatory bowel disease or to treat or prevent septic
shock. The antagonists can also be used to treat meningococcemia, inflammation, bacterial
infections, cachexia and cerebral malaria. The products can also be used for detection and
diagnosis.

L9: Entry 23 of 23

File: DWPI

Dec 30, 1998

DERWENT-ACC-NO: 1999-059802
DERWENT-WEEK: 199918

TITLE: New isolated human tumour necrosis factor receptor-like protein 8 - used to develop products
for treating e.g. tumours, immunodeficiencies , autoimmune diseases, septic shock, inflammation or
infections

ABTX:
USE - The TR8 receptor is a tumour necrosis factor (TNF) receptor like polypeptide. The TR8 receptor
is involved in e.g. cell proliferation , hematopoeitic development, osteoclast differentiation, and
survival of dendritic cells. Soluble fragments of a TR8 polypeptide can be used to treat herpes
simplex viral infection (claimed). TR8 proteins or agonists or antagonists can be used for treating
a disease state associated with aberrant cell survival (claimed). Diseases associated with increased
cell survival, or the inhibition of apoptosis, include cancers (e.g. follicular lymphomas,
carcinomas with p53 mutations, and hormone-dependent tumours), autoimmune disorders (e.g. systemic
lupus erythematosus and immune-related glomerulonephritis rheumatoid arthritis) and viral infections
(e.g. herpes viruses, pox viruses and adenoviruses), information graft versus host disease, acute
graft rejection, and chronic graft rejection. Diseases associated with decreased cell survival, or
increased apoptosis, include AIDS, neurodegenerative disorders (e.g. Alzheimer's disease,
Parkinson's disease, Amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration),
myelodysplastic syndromes (e.g. aplastic anemia), ischemic injury (e.g. as caused by myocardial
infarction, stroke and reperfusion injury), toxin-induced liver disease (e.g. as caused by alcohol),
septic shock, cachexia and anorexia. The TR8 receptor agonists may be used to stimulate ligand
activities such as inhibition of tumour growth and necrosis of certain transplantable tumours, or
alternatively, the survival of certain cell types (e.g. dendritic cells (DCs)). The agonists may
also be used to stimulate cellular differentiation, e.g. T cells, osteoclasts, fibroblasts and
hematopoietic cell differentiation. Agonists to the TR8 receptor may also augment TR8's role in the
host's defense against microorganisms and prevent related diseases (infections such as that from
Listeria monocytogenes) and Chlamidiae. The agonists may also be used to protect against the
deleterious effects of ionising radiation produced during course of radiotherapy, such as
denaturation of enzymes, lipid peroxidation, and DNA damage. They may also be used to mediate an
anti-viral response, to regulate growth, to mediate the immune response and to treat
immunodeficiencies related to diseases such as HIV by increasing the rate of lymphocyte
proliferation and differentiation. The agonists can also be used to treat bone fractures, defects
and disorders which result in weakened bones such as osteoporosis, osteomalacia, and age-related
loss of bone mass. The antagonists to the polypeptides may be used to inhibit ligand activities,
e.g. stimulation of tumour growth and necrosis of certain transplantable tumours, and promoting the
survival of certain cell types (e.g. DCs). They may also be used to inhibit cellular differentiation
e.g. T-cell, osteoclast, fibroblast, and hematopoietic cell differentiation. They may also be used
to treat autoimmune diseases, e.g. graft versus host rejection and allograft rejection, T-cell
mediated autoimmune diseases such as AIDS or diabetes or for treating inflammatory diseases e.g.
rheumatoid arthritis, osteoarthritis, psoriasis, septicemia, inflammatory bowel disease or to treat
or prevent septic shock. The antagonists can also be used to treat meningococcemia, inflammation,
bacterial infections, cachexia and cerebral malaria. The products can also be used for detection and
diagnosis.